Vitamin D

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Medical Biochemistry & Molecular Biology

Lecture key points

1. Steps of vitamin D synthesis & activation
2. Mechanism of action of vitamin D and its role of calcium hemostasis
3. Vitamin D deficiency clinical disorders

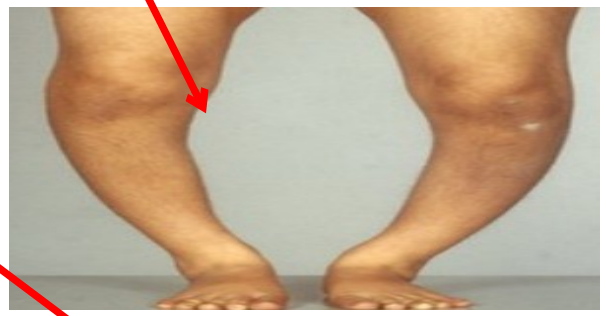
INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture , the student will be able to:

1. Illustrate steps of vitamin D synthesis & activation
2. Discuss mechanism of action of vitamin D and its role of calcium hemostasis
3. Correlate vitamin D deficiency to clinical disorders

Case scenario

A 18 month old boy rarely exposed to sun presents to pediatrician with repeated lower respiratory tract infection (LRTI), developmental delay bowing of the legs and delayed teeth eruption. Physical examination revealed the following:



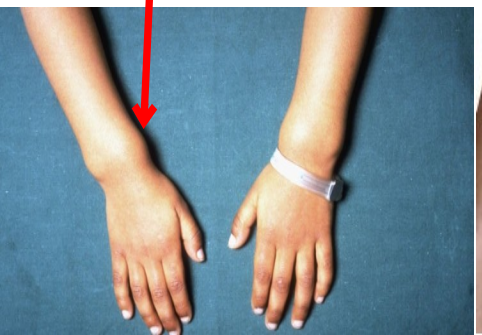
- Anterior fontanel was wide open

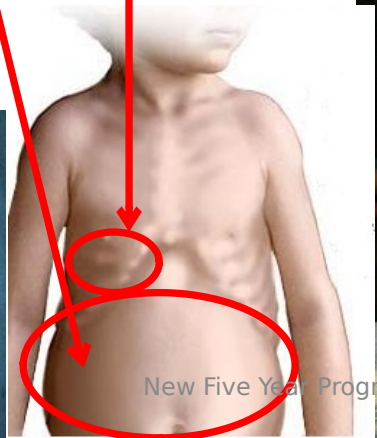
-Bossing of forehead

-Ricketic rosary

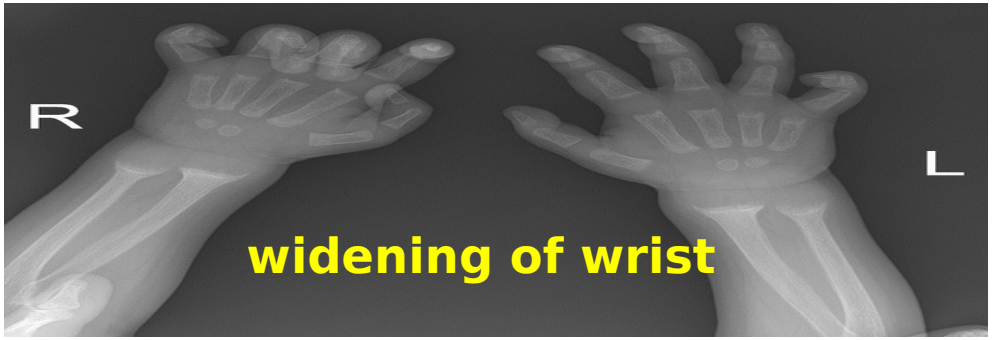
-Pot belly (protruded abdomen)

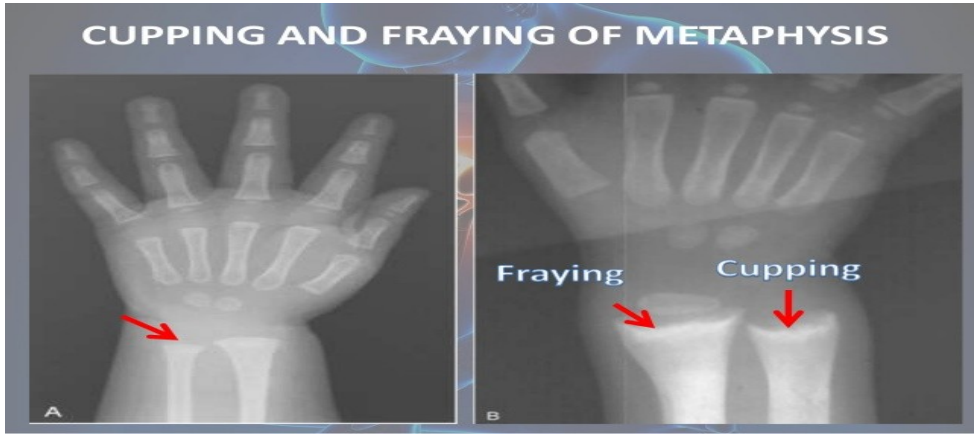
-Doubling of malleoli and widening of wrist were present.

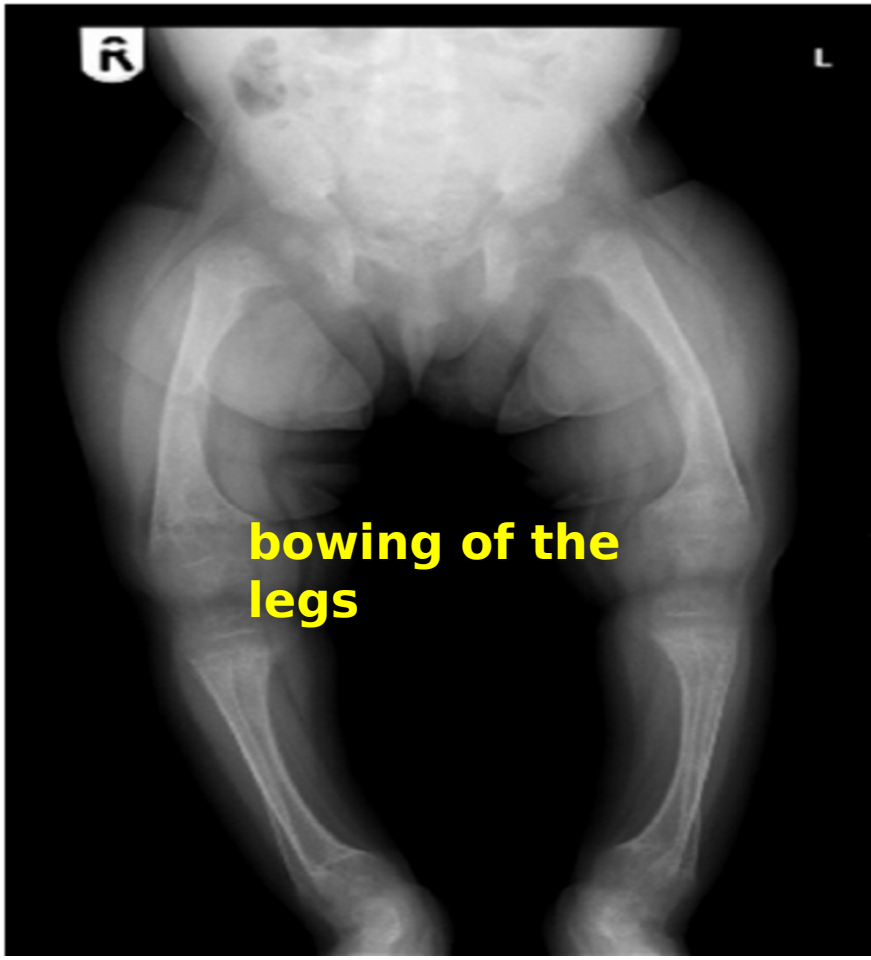




:X-Ray revealed the following







❖X-ray was suggestive of rickets

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https://www.researchgate.net/profile/Benjamin_Jacobs/publication/222125692/figure/fig1/AS:305264826830858@1449792214690/ray-of-2-year-old-boy-with-rickets.png

Case scenario

Laboratory Investigations of blood revealed the following:

- Alkaline phosphatase level was raised
- Ionized calcium level was low
- Phosphorus level was normal
- Vitamin D (25-hydroxyvitamin) level was low
- Parathyroid hormone (PTH) level was high

Case scenario

After that the doctor start treatment of this boy with 1,25 Vitamin D (Calcitriol) & Oral Calcium over several months with adequate sun exposure. After that, there is an improvement of gait & growth.

https://www.biocare.co.uk/media/magpleasure/mpblog/list_thumbnail_file/a/8/cache/1/ece9a24a761836a70934a998c163f8c8/a8a28ddc8da2561494ad663d983332f8.jpg

What is the deficent Vitamin in this boy??

Vitamin D

It is a lipid soluble vitamin

It includes ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3).

Vitamin D (Anti-Rickets) (Anti-osteomalcia)

CHEMISTRY: **Lipid soluble vitamin**

- It is a ***steroid prohormone*** which is converted in the body to a **hormone (calcitriol).**

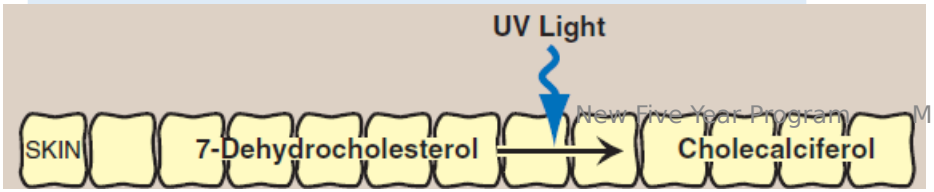
It includes:

- **Ergocalciferol** (**vitamin D2**): **found in vegetables & yeast**
- **C** **found in e c**

Sources of vitamin D?

Endogenous

Vitamin D3 (Cholecalciferol) is produced in the skin by UV irradiation of 7-dehydrocholesterol,an intermediate in cholesterol synthesis, present in subcutaneous .fat



Exogenous dietary=

Animal sources: provide vit D3 (Cholecalciferol) (egg yolk, cod liver oil, salmon fish &fortified milk)

Plant source e.g:Yeast

provide vitamin D2 (ergocalciferol)

Activation of Vitamin D

- **Vitamins D3 (and D2) are converted in vivo to the active form of the vitamin D by two sequential hydroxylation reactions:**

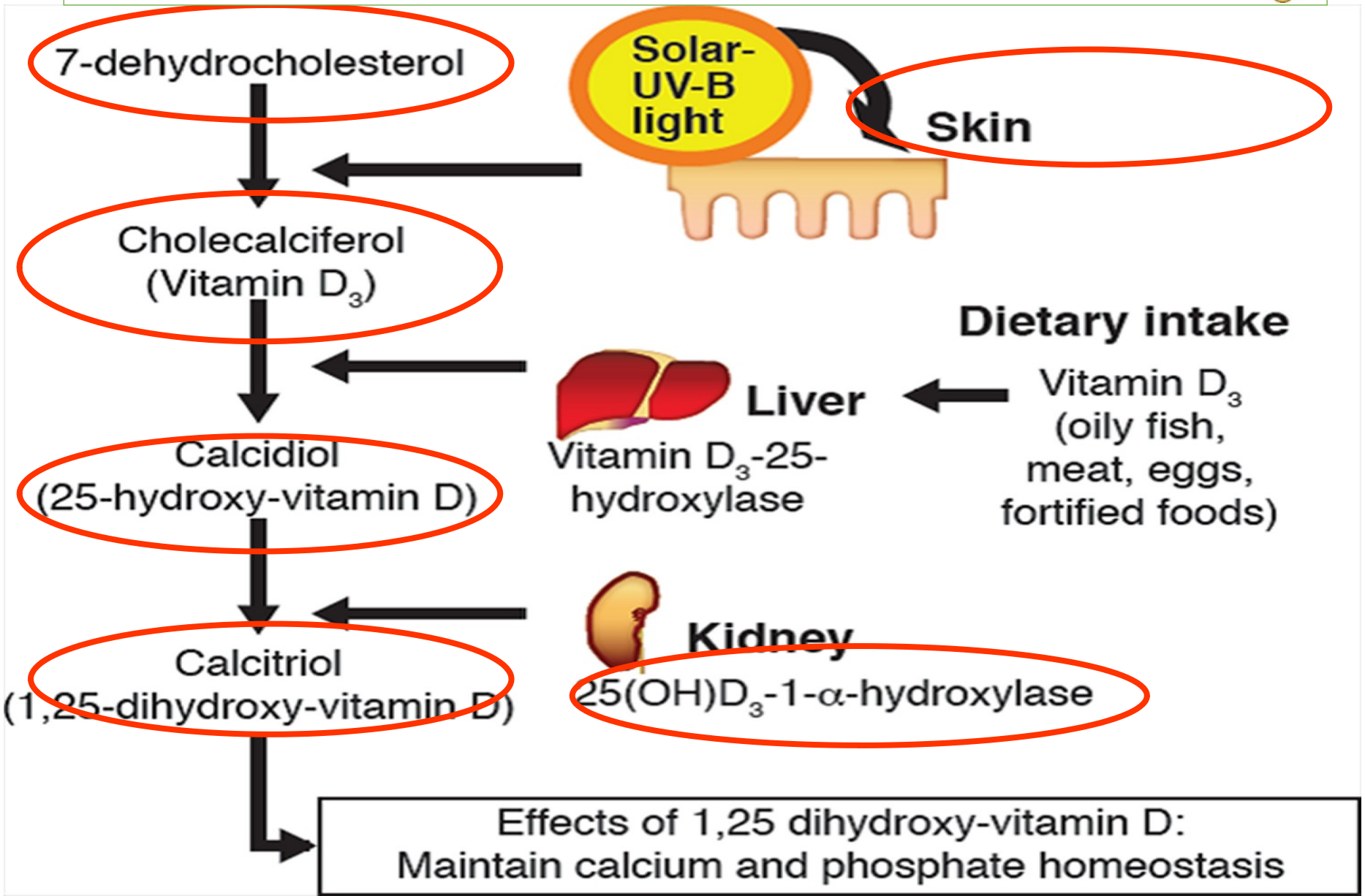
- **The first hydroxylation occurs in the liver, at Carbon number 25 (C25).**

- The product of the reaction, 25-hydroxycholecalciferol {(25-OH-D3),calcidiol} ,which is the predominant form of vitamin D in the plasma and the major storage form of the vitamin.

- **The second hydroxylation occurs in the kidney, at C1 position :**

25-OH-D3 is further hydroxylated at C1 position by a specific 1α hydroxylase found primarily in the kidney, resulting in the formation of 1,25-dihydroxycholecalciferol (calcitriol)=active form of vit.D

How Vitamin D is activated??



Regulation of Vitamin D activation

- **Formation of active vitamin D is tightly regulated by the level of plasma phosphate and calcium ions.**

- **This regulation occurs on kidney**

1α-hydroxylase

Regulation of vitamin D

1- ↓ plasma phosphate directly increases 1α-hydroxylase activity.

2- ↓ plasma calcium indirectly increases 1α-hydroxylase activity by triggering the → release of parathyroid hormone (PTH)

Directly stimulate 1α-hydroxylase

Regulation of vitamin D

3.↑↑ calcitriol (1,25-diOH-D3), the product of the reaction, decreases 1α-hydroxylase activity.

4. Growth hormone, estrogen, and prolactin also stimulate 1α-hydroxylase

This increases the rate of vitamin D activation in growing children and in pregnant and lactating women.

Factors regulating blood Ca ++

Normal serum calcium: 9 - 11 mg/dl

1) Hormonal regulation of blood Ca ++:

A) Hormones that increase blood calcium level:

1- PTH

2- 1,25-dihydroxycholecalciferol or 1,25-dihydroxyvitamin D3(calcitriol)

B) Hormone that decreases blood calcium level :

1- Calcitonin

How active vitamin D regulate the plasma levels of calcium??

The overall function of 1,25-dihydroxycholecalciferol (calcitriol)

is to maintain normal plasma levels of calcium

HOW??

Function of vitamin D

(A) Vitamin D (calcitriol) function in Ca metabolism

(1) Effect of active vitamin D on intestine:

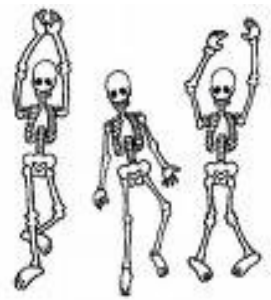
It stimulates **Ca^{2+} and phosphorus absorption** by **increasing synthesis of a specific calcium-binding protein (Calbind) (through genetic level).**

(2) Effect of active vitamin D on kidney:

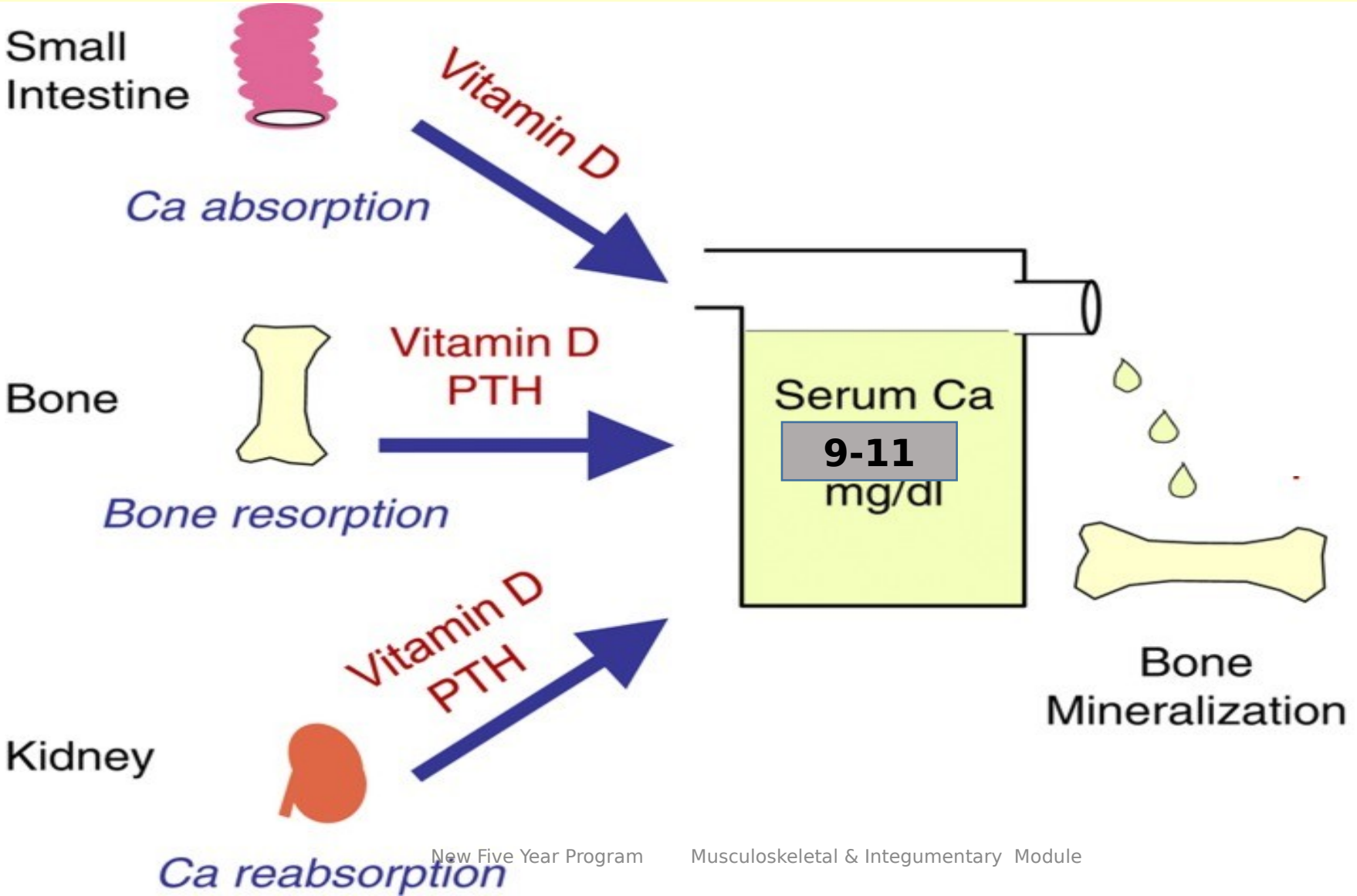
It stimulates renal reabsorption of Ca^{2+} in distal tubules.

3) Effect of active vitamin D on bone mineral turnover:

When blood calcium decrease increase of D which acts with parathormone to promot resorption (demineralization.)



Effect of vitamin D on plasma levels of calcium??



Disorders of Calcium metabolism

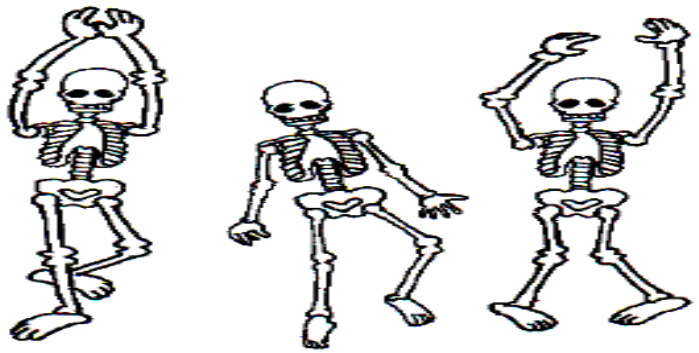
1) Hypocalcaemia:

Diagnosed when serum Ca level is below 7.5 mg/dl

2)Hypercalcaemia:

Diagnosed when serum Ca level is above

11 mg/dl



Causes of Hypocalcemia :

1)Hypoparathyroidism

2)Vitamin D deficiency

3)Renal disease:

(↓activation of Vitamin D &↑excretion of calcium)

4) Inadequate intake

5) Defect in intestinal absorption

Clinical picture of Hypocalcemia:

1- Muscle cramps

2- Tetany

3- CVS : abnormal ECG

4-In chronic cases (bone manifestations):Ricketes, osteomalacia & osteoporosis.

Rickets is defective mineralization or calcification of bones before epiphyseal closure (remember the case (boy).

Rickets & Oseotomalcia

- Osteomalacia is Demineralization of preexisting bones (after epiphyseal closure).
- Occurs in adults especially pregnant and lactating female due to chronic deficiency calcium ,vitamin D deficiency or defects ,or increase utilization as frequent multiple pregnancy.

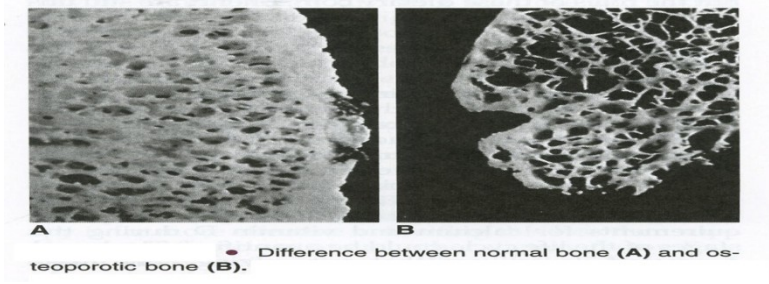
The patients of osteomalacia presents with :

- Diffuse joint and bone pain (especially of spine, pelvis, and legs)
- Muscle weakness.
- Difficulty walking, often with waddling gait.
- Hypocalcemia
- Compressed vertebrae and diminished stature.
- Weak, soft bones & insufficient mineralization of the bone.
- increased susceptibility to bone fractures.
- X ray showing
- Decreased bone mineralization

Treatment:

- 1,25-diOH-D3 (calcitriol) administration
- Calcium administration

Osteoporosis



Difference between normal bone (A) and osteoporotic bone (B).

- It is common in females after *menopause*.

-It is characterized by **generalized aches and bone pains & easy fracture & X-Ray (**decrease in both bone mineral and bone matrix).

-**No estrogen** → **No** stimulation 1α-hydroxylase. Treated by hormonal replacement therapy (estrogen),vitamin D & Calcium

Causes of hypercalcemia:

1) **Hyperparathyroidism:**
 - Parathyroid adenoma
 - PTH secreting tumor

2) ↑release of Ca from bones as in primary or secondary bone tumors

3) Vitamin D toxicity [*Note:* Toxicity is only seen with use of supplements.]

4) Calcium therapy

Clinical picture of hypercalcemia:

Hypercalcemia charecterized by deposition of calcium in many organs, particularly the arteries and kidneys.

1- Kidney: Nephrocalcinosis & renal calculi

2-GIT:Anorexia , nausea & vomiting

3-CVS:Arrythmia

4-Muscles:Hypotonia

5-CNS:Confusion,irritability &depression

6-Bones:Excess mineralization & marble bone disease

Renal Rickets "renal osteodystrophy":

- When **renal parenchyma is lost** or diseased → Deficiency of 1α hydroxylase enzyme → 1,25 $(OH)_2$ D_3 is not formed → Hypocalcaemia →↑ secretion of parathyroid hormone →↑ demineralization of bone → clinical manifestations like that in rickets.
- This case is **does not respond to vitamin D_2** administration.
- **Calcitriol** (active form) must be given in this case

Lecture Quiz

Which one of the following vitamins is useful for postmenopausal women?

A. Vitamin D

B. Vitamin K

C. Vitamin C

D. Folic acid

Lecture Summary

1. Steps of vitamin D synthesis & activation
2. Mechanism of action of vitamin D and its role of calcium hemostasis
3. Vitamin D deficiency clinical disorders

SUGGESTED TEXTBOOKS

- "Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R.Ferrier
- "Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W.Rodwell.
- Fundamentals of Clinical Chemistry (Tietz) Sixth
- "Textbook of Biochemistry with Clinical Correlations" by T.M.Devlin
- *www.namrata.co- Biochemistry for medics*

Thank you

Dr/Amal El-Shal